Human Immunodeficiency Virus Infection and Hodgkin Lymphoma in Southern Africa

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1 Introduction

Hodgkin lymphoma is a malignancy of lymphoid cells first described by Hodgkin (1832). By the turn of the century, Sternberg (1879) and Reed (1902) provided early descriptions of the pathological characteristics of the disease. More recently, it has become clear that the Reed-Sternberg cell is derived from clonal B-cells (post-germinal center B-cells), giving credence to the malignant nature of Hodgkin disease, and hence the preferred term of Hodgkin lymphoma – HL (Marafioti et al., 2000).

Over the past few decades, significant advances have been made in the biology and management of HL. More than 70% of patients with HL are curable (especially those presenting with early stage disease). Better insight has been gained with regard to the short and long term toxicities of chemotherapy and radiotherapy. Furthermore, the advent of new imaging techniques such as PET (positron emission tomography)-scans are allowing therapy to be individualized and tailored in a risk adapted and response adapted fashion (Evens & Horning, 2011).

The incidence of HL (approximately 1 – 3.5/100,000), varies widely throughout the world, based on geographical and ethnic factors. The highest rates of HL are seen in the United States, Canada and Europe, with much lower rates occurring in Japan, Korea and China. HL is more common in males compared to females, with a male to female ratio of approximately 1.5:1. HL occurs most often in young adults, with a peak frequency in the third decade of life. A bimodal age distribution may be seen, with a second age peak noted in the 6th to 8th decades (Katanoda & Yako-Suketomo, 2008; Correa & O’Connor, 1971; Macfarlane et al., 1995).

One hundred and eighty years later, the exact aetiology of HL remains unknown. An increased risk of HL is seen with Epstein-Barr Virus (EBV) infection, congenital and acquired immunodeficiency states (such as Human Immunodeficiency Virus – HIV infection / AIDS-Acquired Immunodeficiency Syndrome, post solid organ and haematopoietic stem cell transplantation) and autoimmune disease (Brousset et al., 1993; Herida et al., 2003; Biggar et al., 2006; Hessol et al., 1992; Landgren et al., 2006; Patel et al., 2011; Spina et al., 2011). There is also a tendency for HL to exhibit familial aggregation (Hjalgrim et al., 2004).

HL occurs with increasing frequency in association with HIV, based on linkage and cohort studies. The relative risk is approximately 10-15 fold higher compared with the general population (Herida et al., 2003; Biggar et al., 2006; Hessol et al., 1992; Patel et al., 2011; Spina et al., 2011; Lyter et al., 1995; Goedert et al., 1998; Carbone et al., 2009). The emerging increase of HL in the HIV seropositive population/people living with HIV/AIDS (PWHA) in southern Africa will be highlighted in this review, and the differences compared to HL in developed countries will be described.

2 HIV Lymphoma

Lymphomas occur with an increased frequency in PWHA (Lyter et al., 1995; Goedert et al., 1998; Ziegler et al., 1982). Typically, these lymphomas are aggressive, B-cell NHL’s (Non-Hodgkin Lymphomas), such as diffuse large B-cell lymphoma and Burkitt or Burkitt-like lymphoma (Goedert, 2000; Ziegler et al., 1984), whereas, the indolent lymphomas tend to be more sporadic, and based on the AIDS Lymphomas...
ma Registry, account for <3% of all lymphomas occurring in HIV seropositive patients (Levine et al., 2002). NHL is the most common malignancy in the post cART (combination antiretroviral therapy) era in PWHA, superseding Kaposi’s Sarcoma. The incidence of NHL in resource-rich settings has decreased in the post cART era compared to the pre cART era (Ziegler et al., 1982; Ulrickson et al., 2012). However, the contrary is true in resource-poor settings, with a noticeable increase in NHL incidence (Ulrickson et al., 2012; Patel et al., 2007; UNAIDS, 2008; Casper, 2011). This is particularly true of sub-Saharan Africa - the epicenter of the HIV pandemic and South Africa, which is home to over 5 million PWHA (UNAIDS, 2008). Indeed, NHL is now the commonest haematological malignancy in South Africa, in the current HIV/AIDS era and the number of seropositive patients continues to increase.

In Africa, the HIV/AIDS epidemic was first reported in 1984 (Clumeck et al., 1984). The major risk of HIV in Africa occurs in/heterosexual relationships, and accounts for an approximately equal male to female ratio, as compared to the Western world in which the major risk groups involve intravenous drug use and homosexual relationships, thus predominantly affecting males. Furthermore, early in the HIV epidemic, there was no marked increase in the incidence of NHL compared to the USA. This was attributed to PWHA dying earlier in the course of their disease possibly from infectious complications such as pneumonia and tuberculosis. The decreased longevity prevented the subsequent or later development of NHL. In addition, there may be underreporting of lymphoma or the missed diagnosis of lymphoma, with a diagnosis of an infective cause of lymphadenopathy (such as tuberculosis) being favored over lymphoma, especially in the absence of performing a fine needle aspirate or more particularly a lymph node biopsy (Clumeck et al., 1984; Parkin et al., 1999; Adeniji & Anjorin, 2000).

Chris Hani Baragwanath Academic Hospital (CHBAH) is a large, tertiary, public sector, University of the Witwatersrand linked hospital, located in Soweto, Johannesburg. The first patient with HIV-HL was seen at CHBAH in 1994. Since then, there has been a modest increase in HIV-HL up to 2006. In a study by Stein et al, (2008), the percentage seropositivity of HL in a South African cohort (which included patients from CHBAH) was 19.5% (OR = 1.6, 95% CI = 1.0 – 2.7), during the period 1995 – 2004. However, in the last 5 years (2007 – 2011) at our single institution, the percentage HIV seropositivity in HL is greater than 50% (see Figure 1) and the number of patients over the years are gradually increasing (see Figure 2). From 1992 – 2001, the average number of new patients diagnosed with HL was 12/year. However, in the latter 10 year period (2002 – 2011), the average number has increased to 18/year, representing a 52% increase (personal, unpublished data). Thus, the focus of this review relates to the emerging problem of Hodgkin lymphoma in the setting of HIV in southern Africa.

3 Hodgkin Lymphoma and HIV

3.1 Epidemiology

HIV-HL manifests with distinct differences compared to HL in the general population. It is generally more aggressive, presents with advanced stage disease, frequent constitutional (“B”) symptoms, less favourable histology, more frequent bone marrow involvement and overall a poorer prognosis compared to immunocompetent individuals (Patel et al., 2011; Spina et al., 2011).

With the advent of HAART (highly active antiretroviral therapy), now referred to as cART (combination antiretroviral therapy), the AIDS related morbidity, particularly with respect to opportunistic infections has decreased and the survival of HIV/AIDS patients has increased (Ribera et al.,
**Figure 1:** HIV seropositive and HIV seronegative patients with Hodgkin Lymphoma from 1990 to 2011 seen at Chris Hani Baragwanath Academic Hospital

**Figure 2:** Total number of patients with Hodgkin Lymphoma seen at Chris Hani Baragwanath Academic Hospital from 1990 - 2011
In the post cART era, ADCs (AIDS-defining cancers) continue to fall, but the rates of NADCs (non-AIDS defining cancers) such as HL, anal carcinoma, lung carcinoma and skin cancers are on the increase (Crum-Cianflone et al., 2009). With HL, there is an increasing relative risk of approximately 10 - 15 fold, compared with the general population (Herida et al., 2003; Biggar et al., 2006; Hessol et al., 1992; Spina et al., 2011; Lyter et al., 1995; Goedert et al., 1998; Carbone et al., 2009).

Based on a number of epidemiological studies conducted in the last two decades, and summarised by Carbone et al., (2009), there is clear evidence that HIV positive individuals have a higher risk of developing HL compared to their HIV negative counterparts. This is in contrast to HIV-NHL or HIV-Kaposi’s sarcoma (where the incidence of the disease has decreased significantly after the introduction of cART). However, cART has allowed the use of standard therapeutic options to be delivered to seropositive patients in a more optimal manner, bringing about renewed optimism in the management of such patients. cART use is associated with higher CD4 T cell counts and enhanced immunity. Thus, despite the benefit of cART, which improves immunity and decreases the risk of opportunistic infections, there is a paradoxical increased risk of HL. It is postulated that the improved CD4 T cell count that occurs post cART use, provides anti-apoptotic pathways and mechanisms for immune escape by tumour cells, thus resulting in an increased risk of HL.

However, in contrast to this, a 20-year cohort study has shown that with the advent of antiretroviral therapy, ADCs (AIDS-defining cancers) continue to fall, but the rates of NADCs (non-AIDS defining cancers) are on the increase. It is suggested that this increase appears to be more related to the aging of the HIV population (i.e. increased longevity allowing a greater risk of developing lymphoma) rather than the antiretroviral therapy and its effect on the CD4 T cell count (Crum-Cianflone et al., 2009).

### 3.2 Pathogenesis

The Reed-Sternberg (RS) cell is the pathological hallmark of HL. Histologically, HL is characterized by a population of RS cells, which constitute < 1 – 2% of the cellular component, admixed with a reactive, mixed inflammatory infiltrate of eosinophils, lymphocytes, plasma cells and histiocytes. Cytokines and chemokines are produced by either the RS cells or the reactive cells in the background microenvironment of the tissue. The cytokine production may explain the presence and maintenance of an impaired immune response, while the chemokines (cytokines with chemoattractant properties) play a role in leucocyte trafficking, attract chemokine receptor CCR4-expressing Th-2 cells and T regulatory cells, and allow a favourable environment for survival of RS cells (Takegawa et al., 2008; Niens et al., 2008; Maggio et al., 2002). Cross talk between the RS cells and reactive cells mediated by cytokines such as IL-13, IL-17, IL-10, transforming growth factor-beta and chemokines - principally CCL17 (thymus and activation-regulated chemokine, TARC) and CCL22 (macrophage-derived chemokine, MDC), lead to an environment where RS cells are able to proliferate, escape from apoptosis and survive host anti-tumour defense (Takegawa et al., 2008; Niens et al., 2008; Maggio et al., 2002). The CD4+ T cells surrounding the neoplastic cells in HL are CD45RO+/CD45RA-/CD45RBdim, suggesting a memory Th2 phenotype (Poppema et al., 1996). The association between HIV and EBV and HIV and HL brings into question the pathogenetic role of EBV in HIV-HL. HIV-associated immunosuppression allows the unchecked and uncontrolled proliferation of Epstein-Barr virus (EBV) infection. Cellular immunity plays a major role in the control
of EBV infection. In the initial phase of infection, proliferation of EBV-infected B-cells is controlled by suppressor T cells, natural killer cells and non-specific cytotoxic T cells. Later in infection, HLA (human leukocyte antigen) restricted cytotoxic T cells are generated that recognize EBNAs (EBV nuclear antigens) and LMPs (latent membrane proteins) and lead to the destruction of EBV infected cells (Cohen et al., 2008). Therefore, where HIV exists and T cell immunity is compromised, EBV-infected cells may begin to proliferate. A high frequency of EBV incorporation (80 – 100%) is noted in the tissues of patients with HIV-HL, with the EBV genomes being episomal and clonal in such cases (Rezk & Weiss, 2007, Carbone et al., 1999). EBV transforming proteins, such as LMP-1, is expressed in virtually all HIV-HL patients (Carbone et al., 1999; Young & Rickinson, 2004; Carbone et al., 2008). The expression of EBV-LMP-1 is important in the pathogenesis of HIV-HL. LMP-1 expression by EBV-infected RS cells represents the principal mechanism for constitutive NFκB activity, which confers an apoptosis resistant phenotype to the RS cells (Carbone et al., 1999; Young & Rickinson et al., 2004; Carbone et al., 2008). EBV-immortalized B cells also produce CCL17 and CCL22 through LMP-1 mediated activation of NFκB (see details above). Furthermore, LMP-1 has oncogenic potential by enhancing bcl 2 expression and by acting via the CD40 signalling pathway (which enhances NFκB activity) to evade apoptosis (Carbone et al., 1999; Young & Rickinson et al., 2004; Carbone et al., 2008; Nakayama et al., 2004). Thus, HIV-HL appears to be an EBV-related lymphoma, based on the expression and contribution of LMP-1 to lymphomagenesis.

RS cells of classical HL represent transformed B cells (post germinal center B-cells) that originate from preapoptotic germinal center B cells. They express CD15 and CD30 as well as LMP-1 and display a BCL6-/CD138+/MUM1/IRF4+ (Interferon Regulatory Factor-4) phenotype (Carbone et al., 1999; Klein & Dalla-Favera, 2008; Carbone et al., 2001). CD68 detects infiltrating macrophages, and, if strongly positive, confers an adverse prognosis. In addition, LMP2A and EBNA-1 may also contribute to the development of the RS cells and are expressed in the RS cells of this tumour (Young & Rickinson, 2004; Carbone et al., 2008). LMP2A may promote the survival of the “crippled” germinal center B-cells, thereby aiding in their development (Mancao & Hammerschmidt, 2007).

### 3.3 Clinical Presentation

HIV-HL patients display a more aggressive clinical course than their seronegative counterparts. The behaviour of the disease is different, and based on a number of studies (Andrieu et al., 1993; Berenguer et al., 2008; Carbone et al., 2009; Chimienti et al., 2008; Garcia-Noblejas et al., 2007; Rubio, 1994; Tirelli et al., 1995; Tirelli et al., 1987; Vaccher et al., 2003), the following characteristics are noted: more frequent constitutional “B” symptoms – 70 – 96%; more advanced stage disease (III and IV) – 74 – 92%; more frequent involvement of extranodal sites – 17 – 62%; with bone marrow involvement being the most common extranodal site – 40-59%; followed by involvement of the liver – 17 – 40% and spleen – 20 – 30%. The vast majority (> 80%) of the patients were males. The median age at presentation was approximately 34 years. The median CD4 count was mostly in the intermediate range of 240-306/µl. Compared to HIV negative HL, where nodular sclerosis is the dominant histological subtype, mixed cellularity is most commonly encountered in HIV-HL – 33 – 53% (Berenguer et al., 2008; Carbone et al., 2009; Chimienti et al., 2008; Fazel, 2012; Patel, 1994; Patel et al., 2011). Nodular sclerosis is the second most common histological subtype in HIV-HL – 24 – 31%. However, with more severe immunosuppression, nodular sclerosis becomes less frequent (Takegawa et al., 2008). There is also an
increasing number of patients with lymphocyte depleted histology – 8 – 20% in HIV-HL (Berenguer et al., 2008; Carbone et al., 2009; Chimienti et al., 2008; Patel et al., 2011).

Based on the Italian Cooperative Group on AIDS and Tumors (GICAT) study, in comparison with patients who were cART naive, patients receiving cART before the onset of HL are older, have less B symptoms, have higher leukocyte and neutrophil counts and have a higher haemoglobin level (Chimienti et al., 2008). In a recent review of 43 patients (29 of whom were HIV seropositive) with HL seen at CHBAH over a 2 year period (July 2008 – June 2010) a number of striking similarities and differences were noted when comparing the seropositive patients in this cohort with other published studies outside of Africa (Patel et al., 2011). The median age at presentation of 38 years was similar to other series. There was no striking male predominance. Conversely, the male to female ratio is almost equal at 1.1:1. All the patients had heterosexual acquisition of HIV. None of the patients acquired their HIV through intravenous drug use or homosexual contacts. This is different to other series where homosexuality and intravenous drug use are significant, documented risk groups (Berenguer et al., 2008; Carbone et al., 2009; Chimienti et al., 2008; Hessol et al., 1992; Lyter et al., 1995; Mancao & Hammerschmidt, 2007;). The presentation with advanced stage disease (82%), more frequent “B” symptoms (93%), more frequent involvement of extranodal sites (bone marrow – 38%; liver – 45%; spleen – 28%) and “true” extranodal sites (17%) and the histological pattern of disease (mixed cellularity being the most common) is similar to that reported in the literature. The median CD4 count of 176/µl (range 10 – 407) is generally lower (and is likely to be a reflection of advanced HIV infection), although there are series reported of HIV-HL with median CD4 counts of < 200/µl (Tirelli et al., 1987). In the series by Thompson et al. (2004), the mean CD4 count was 154/µl (an indication of later stage HIV infection), and in addition, there was inversion of the CD4/CD8 ratio in all the patient’s tested. In this study, the inversion of the CD4/CD8 ratio appeared to be a better predictor of HIV infection in HIV-HL than the p24 immunoreactivity, which was present in only 17% of the patients.

In our series 12/29 (41%) of the patients had newly diagnosed HIV, i.e. at the time of the diagnosis of HL. In 62% of the patients, the duration of the diagnosis of HIV (including new patients was < 1 year). Only 45% of the patients were on antiretroviral therapy at diagnosis of HL, compared to 71-80% in other series (Berenguer et al., 2008; Carbone et al., 2009; Chimienti et al., 2008). A further striking difference is the high proportion of patients with Tuberculosis (TB) in this series – 59% (38% with active disease and 21% with past, documented disease). The high prevalence of TB may be a reflection of the more severe immunosuppression in the patients. Moreover, the association between TB and HL is well documented (Kaplan et al., 1974). TB and HL share similar clinical features, such as the constitutional symptoms, lymphadenopathy, hepatosplenomegaly, cytopenias, bone marrow involvement (including granulomatous reactions), and overlapping CXR and CT scan features. This commonality often leads to a delay in diagnosis of either condition and is clearly exemplified in the case report by Fernando et al. (2009). TB is highly prevalent in PWHA, with South Africa being the epicentre of the co-epidemic (Lawn & Churchyard, 2009). Indeed, both TB and HL may co-exist in patients with HIV. The presence of TB, often in a disseminated fashion, has an adverse impact on the clinical outcome of the patients.

In general, the outcome in our study of the HIV-HL patients was less favourable than the HIV seronegative patients (Patel et al., 2011).

Two prior retrospective studies in HL at CHBAH are worthy of mention (Patel, 1994; Fazel, 2012). In the first study conducted from June 1986 to May 1992, there were a total of 62 patients. All the patients were HIV negative. The mean age of the patients was 35 years (range 12 – 78 years), with a M:F
“B” symptoms were present in 92% of the patients and 72% had stage III or IV disease. The most common histological subtype was nodular sclerosis (50%), followed by mixed cellularity (39%). The CR was 67%. In the second study, 163 patients were seen over a 15 year period (January 1990 to December 2004). The median age was 29 years (range of 13 – 87 years), with a M:F ratio of 1.3:1. The commonest histological subtype was mixed cellularity (45%), followed by nodular sclerosis (37%). Of the evaluable patients, the CR was 63%. 23% were HIV seropositive. Some of the clinical characteristics of the HIV seropositive and seronegative patients in this study are depicted in Table 1.

<table>
<thead>
<tr>
<th>HIV Status</th>
<th>Seropositive</th>
<th>Seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patients = 163</td>
<td>37 (23%) at presentation</td>
<td>116 (71%) at presentation; 5% HIV positive post HL diagnosis; 1% unknown</td>
</tr>
<tr>
<td>Median Age (Range) in Years</td>
<td>30 (13-59)</td>
<td>29 (13-87)</td>
</tr>
<tr>
<td>M:F Ratio</td>
<td>1.8:1</td>
<td>1.2:1</td>
</tr>
<tr>
<td>CD4 Count at Presentation (/Ul)</td>
<td>186 (32-769)</td>
<td>N/A</td>
</tr>
<tr>
<td>“B” Symptoms</td>
<td>77%</td>
<td>78%</td>
</tr>
<tr>
<td>Bone Marrow Infiltration</td>
<td>43%</td>
<td>20%</td>
</tr>
<tr>
<td>Advanced Stage (III &amp; IV) Disease</td>
<td>78%</td>
<td>67%</td>
</tr>
<tr>
<td>“True” Extranodal Disease</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Histological Subtype:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Cellularity</td>
<td>61%</td>
<td>42%</td>
</tr>
<tr>
<td>Nodular Sclerosis</td>
<td>17%</td>
<td>41%</td>
</tr>
<tr>
<td>Other/Unclassifiable</td>
<td>22%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Table 1: Clinical characteristics of HIV seropositive and HIV seronegative patients with Hodgkin lymphoma seen over a fifteen year period (1990 – 2004) at Chris Hani Baragwanath Academic Hospital (adapted and updated from Fazel, 2012)

With regard to the findings of this study, HIV seropositive patients, compared to HIV seronegative patients, have more advanced stage disease, a higher frequency of mixed cellularity subtype, more extranodal disease such as bone marrow involvement and more “true” extranodal disease. In general, the treatment response was less favourable in the seropositive group, in which 25% of the patients died before completion of their course of treatment, 33% defaulted treatment and 42% completed treatment successfully (Fazel, 2012).

### 3.4 Management

The management of HIV-HL is challenging because of the frequency of infections, likelihood of organ dysfunction due to HIV, more frequent bone marrow involvement, increased myelosuppression, potential drug-drug interactions of the antiretrovirals and anti-infectives with chemotherapy, the advanced and widespread nature of the disease at presentation and the preponderance of less favourable histological subtypes. Treatment approaches include vigorous supportive care (c ART, antivirals, antifungals, growth factors such as G-CSF), together with standard multiagent chemotherapy.

Chemotherapy regimens for HIV-HL such as ABVD, EBV, EBVP and MOPP/ABV hybrid are feasible and can be delivered with concomitant cART. The AIDS Clinical Trials Group (ACTG) treated
21 patients with ABVD for 4 – 6 cycles with G-CSF support. Antiretroviral therapy was not used. The complete remission rate (CR) was 43% with a median overall survival of 18 months (Levine et al., 2000). In a more recent Spanish study (GESIDA – Grupo de Estudia de SIDA), 62 patients with HIV-HL received the standard, full-dose ABVD and cART, with 87% of the patients achieving a CR. The 5-year overall survival (OS) and event-free survival (EFS) probabilities were 76 and 71% respectively. The immunological response to HAART had a positive impact on OS (p = 0.002) and EFS (p = 0.001) (Xicoy et al., 2007). Use of cART substantially improves the overall survival in HIV associated HL. This is due to a decrease in the incidence of opportunistic infections, the ability to deliver more appropriate and aggressive chemotherapy on schedule and to the less aggressive presentation of lymphoma in patients on cART, in comparison with those lymphomas that arise in patients who never received cART (Tirelli et al., 1995; Tirelli et al., 1987; Andrieu et al., 1993; Rubio, 1994). In the study of Hentrich et al. (2006), 34/59 patients receiving cART (n = 34) had a significantly better 2-year overall survival than those not receiving cART (74% versus 30%, p < 0.001). The advent of cART also allows for more aggressive treatment options such as VEBEP (Spina et al., 2003), BEACOPP (Hartmann et al., 2003), Stanford V (Spina et al., 2002) and the use of high-dose chemotherapy and autologous stem cell transplantation (ASCT) in selected patients (Krishnan et al., 2005, Spitzer et al., 2008). However, in general, response rates and cure rates are lower than in HIV seronegative patients, despite the substantial progress made in the last decade. The challenge at present is to optimise the use of standard approaches as used in HIV negative HL. Once this is established in this population, evaluation of experimental and newer therapies will follow.

The role of PET/CT in HIV-HL is unclear. \(^{18}\)F-FDG (Fluoro-2-Deoxy-D-Glucose)-PET/CT is recommended for the initial staging and treatment response in HIV seronegative HL, which typically demonstrates \(^{18}\)F-FDG-avid disease (Juweid & Cheson, 2005). A recent trend in the management of HL is to assess the response to treatment after two cycles of ABVD, based on the PET/CT scan (Gallamini et al., 2006). A negative PET/CT scan implies a favourable prognosis, generally allowing continuation of treatment, while a positive PET/CT scan may warrant escalation to a more aggressive treatment such as BEACOPP. \(^{18}\)F-FDG-PET/CT may also be used at the end of therapy, to characterize residual masses identified on CT scan, to determine whether they are metabolically active (implying residual disease, requiring further treatment) or inactive (implying fibrosis, not requiring further treatment). However, in the setting of HIV, “false-positives” may occur due to opportunistic infections such as TB, herpes simplex virus etc., as well as with malignancies such as Kaposi’s sarcoma (Goshen et al., 2008; Juweid et al., 2007; Barrington & O’Doherty, 2003). Therefore, a baseline PET/CT scan may be useful in this setting. However, the exact role of PET/CT in HIV-HL requires further evaluation and validation.

### 4 Conclusion

HIV is increasingly being associated with a higher risk of developing HL, a risk that has not lessened despite the introduction and benefit of cART. HL is now being included among the most common NADCs, in the current cART era. The association from being largely coincidental (overlapping and similar age group for both HL and HIV) may now be causal, with the most plausible explanation being attributed to the pathogenetic role of Epstein Barr virus infection.
The recognition of an increasing trend of HIV-HL in resource-poor settings needs to be further highlighted, so that early diagnosis, early recourse to cART and other appropriate supportive therapy such as the liberal use of growth factors and specific therapy such as chemotherapy can be administered to improve survival.

Therapy of HIV associated HL entails using the same therapeutic approaches as in seronegative HL, including standard chemotherapy regimens such as ABVD, and in the salvage setting, autologous stem cell transplantation in selected patients. In general, the prognosis and overall survival still remains poorer in HIV-HL compared to HIV negative HL. The early recognition and treatment of tuberculosis cannot be overemphasized in settings where tuberculosis is endemic. Newer specific treatment approaches for HL may become necessary in the future to improve survival, and will need to be tailored to HIV-HL. At present, there is a growing body of evidence to suggest that HIV-HL is an emerging challenge, particularly in sub-Saharan Africa, the epicentre of the HIV pandemic.

References


